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ADDITION OF 2-(PHENOXYMETHYL)-2-PROPENYLMAGNESIUM CHLORIDE TO EPOXIDES FOLLOWED BY Pd(0)-CATALYZED CYCLIZATION: A ONE-POT SYNTHESIS OF 3-METHYLENETETRAHYDROPYRANS

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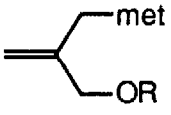
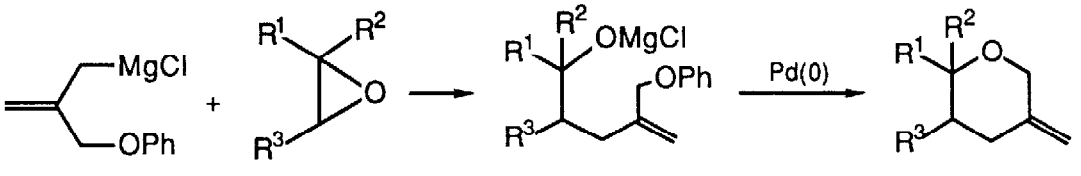
Summary: Addition of 2-(phenoxymethyl)-2-propenylmagnesium chloride to epoxides afforded the ring opening products **3** which were converted by Pd(0) to 3-methylenetetrahydropyrans **4**.

In our one-pot synthesis of five-membered ring compounds, the trimethylenemethane moiety of **1** (met = ZnBr, R = Ph, CH_2Ph) is transferred to 1-silylalkynes,[1] aldehydes and ketones,[2] and imines.[2] When R is allylic or homoallylic, such a process can also occur intramolecularly.[3]



1

Among trimethylenemethane equivalents,[4] 2-(metallomethyl)allyl ethers **1** stand out by their ability to sustain a carbon-metal center of relatively high nucleophilicity. This suggested that **1** (met = MgCl, R = Ph) might be added as a nucleophile to epoxides **2**, whereafter our usual protocol,[1-3] adding a catalytic amount of Pd(0) to the reaction mixture and heating for several hours, might cause the addition products **3** to cyclize, forming 3-methylenetetrahydropyrans **4**.



2 **3** **4**

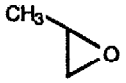
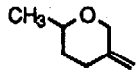
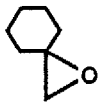
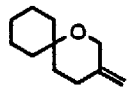
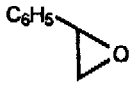
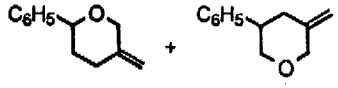
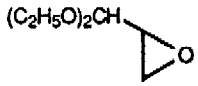
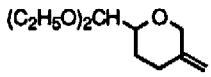
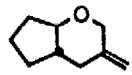
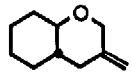
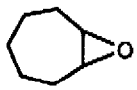
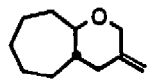
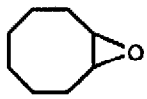
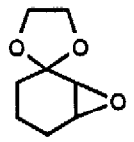
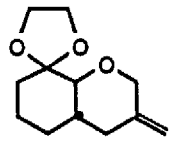
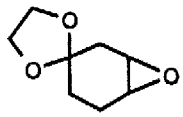
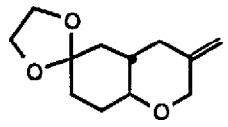
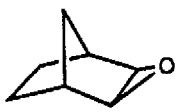
Epoxide ring opening was effected by adding **2** (2-10 mmol) dropwise to a THF solution of **1**[1] (met = MgCl, R = Ph, 1.3 - 1.6 M, 1.2 equiv., 0°C) and stirring the reaction mixture at 0°C for 0.5h and, subsequently, at room temperature for 4h. After addition of 30 mol% $(i\text{-PrO})_3P$ and 5 mol% $Pd(OAc)_2$, which generate Pd(0) *in situ*,[5] the reaction mixture was heated at 70-80°C[6] for 24-48h. Work-up (aqueous NH_4Cl, ether, 1M NaOH, brine, $MgSO_4$, careful evaporation of solvent) and evaporative distillation afforded the desired 3-methylenetetrahydropyrans **4**.[7] Alternatively, the crude reaction product was analyzed by GLC. Results are given in Table 1.

The addition step was a clean reaction[8] yielding only products of *trans* ring opening.[10] Isomerization of epoxides by magnesium halide did not take place. While **2a,b,d,l** are attacked by **1** (met = MgCl, R = Ph) regiospecifically at the unhindered position, predominant α-attack in the case of **2c** conforms with the behaviour of this epoxide towards other Grignard compounds.[11] As indicated by the structure of cyclization product **4j**[12] ring opening of **2j** takes place at the carbon atom closest to the dioxolane ring. Precoordination between the magnesium atom of the organometallic reagent and the oxygen atoms of the dioxolane ring of **2j** may be the reason for this. Even after prolonged heating (48h) at 80°C[6] cyclooctene oxide **2h** and *exo* norbornene oxide **2k** did not react.

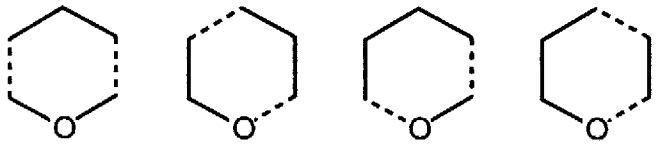
Turning our attention to the cyclization step, we first tried to effect ring closure by means of $Pd(PPh_3)_4$ (5 mol%, 65°C, 24h). Using this catalyst it was found that smooth conversion of **3** to **4** could only be achieved for the magnesium alkoxides derived from the bicyclic epoxides **2e,f,g**. Cyclization of the addition products formed from the monocyclic epoxides **2a,b**, however, required severe reaction conditions (100°C, 70h).[13] With the catalyst system generated *in situ* from $Pd(OAc)_2$ and $(i\text{-PrO})_3P$, most addition products could be cyclized smoothly. Still, ring closure of **3l** and **3j** was very difficult. This may be due to steric hindrance encountered during formation and/or conversion of the π-allyl Pd complex leading to **4** and, in case of **3l**, to extra stabilization of this alkoxy magnesium compound due to intramolecular coordination of the dioxolane ring to the magnesium ion.

Compared to the large number of methods devised for the synthesis of 3-methylenetetrahydrofurans,[14] routes to 3-methylenetetrahydropyrans are few.[15] Our method provides a rather general pathway to these compounds and adds a new [3+3] route (**6**) to the known [3+3][16,17] (**5,6**) and [4+2][16,18] (**7,8**) routes leading to six-membered oxygen heterocycles.

Table 1. 3-Methylenetetrahydropyrans **4** from epoxides **2**.

System	Epoxide **2**	Product **4**	Yield of **4** [a,b] (%)
a			83/--
b			--/94
c		 1 : 4	--/60
d			68/--[c]
e			--/85
f			--/69
g			--/76
h		--[d]	
i			23/--[e]
j			53/--[f]
k		--[d]	

[a] GLC yields. [b] Isolated yields. [c] 60 mol% $(i\text{-PrO})_3P$ + 10 mol% $Pd(OAc)_2$. [d] No ring opening. [e] During ring opening **3l** precipitated from the solution and was dissolved again by addition of DMF (0.3 ml/mmol **3l**). [f] 138 mol% $(i\text{-PrO})_3P$ + 23 mol% $Pd(OAc)_2$.



5 **6** **7** **8**

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6 Reflux temperature of a 1.3 - 1.6 M solution of **1** (met = MgCl, R = Ph) in THF.

7 All new compounds were characterized by NMR and HRMS.

8 Originally, we tried to accomplish ring opening by the method of Linstrumelle[9] (Cu(I)-catalysis, 0.25 M solution of **1** (met = MgCl, R = Ph) in THF, -30°C, 3h). However, this methodology was successful only in case of epoxides **2a,e,f**.

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12 Confirmed by COESY NMR on **4j**.

13 The more rigorous conditions required for cyclization of these compounds may be related to difficulties in achieving the conformation necessary for ring closure, *cf.* S.A. Stanton, S.W. Felman, C.S. Parkhurst and S.A. Godleski, J. Am. Chem. Soc. **105**, 1964 (1983).

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